

Immunogenicity and efficacy of Auxo-GTU[®]-MultiHIV/SIV DNA vaccines in nonhuman primate model of AIDS

Martinson F^{1,2,3}, Dereuddre-Bosquet N^{1,2}, Baron ML^{1,2}, Méderlé-Mangeot I^{1,2}, Culina S^{1,2}, Kaldma K⁶, Sikut R⁶, Männik A⁶, Stanescu I⁵, Ustav M^{4,6}, Le Grand R^{1,2}

1. CEA, Fontenay-aux-Roses, France; 2. Université Paris Sud-11, Orsay, France; 3. INSERM, Paris, France; 4. University of Tartu, Estonia; 5. FIT Biotech, Tampere, Finland; 6. FIT Biotech, Tartu, Estonia

Background

Intradermal (ID) injection of the auxo-GTU[®]-MultiHIVB DNA vaccine induced strong and durable (>3 years) anti-HIV T-cells responses in macaques (Fig.1). Vaccine immunogenicity was significantly enhanced when local electroporation (EP) was associated to ID injection (Fig.2 and Fig3). We used an equivalent auxo-GTU[®]-MultiSIV vaccine to assess its efficacy after SIVmac251 mucosal challenge in macaques.

Methods

1. Auxo-GTU[®]-MultiHIVB vaccine encodes a fusion proteins of Gag, Nef, Tat, Rev and Env/Pol CTL eptiopes of clade B HIV-1

2. Auxo-GTU[®]-MultiSIV vaccine encodes Gag, Nef, Tat, Rev and Env/Pol CTL epitopes of SIVmac239.

3. Vaccination:

- 1 mg at weeks 0, 4 and 12,
- 6 cynomolgus macaques (MHC CI and CI characterized) by classical ID route
- 8 cynomolgus macaques (MHC CI and CI characterized) by the ID combined with EP (6 pulses of 10 μs with 300-600 mA at 90 μs intervals using Nepa Gene™)

4. Challenge:

1. By the rectal route (50 AID50)
2. Uncloned and pathogenic SIVmac251
3. Week 29:
 - 6 animals of each vaccinated group
 - 6 Controls
4. Week 72:
 - 2 animals of group ID+EP
 - 5 Controls
 - have been challenged at week 72.

Results

Before challenge:

All vaccinated animals raised SIV-specific T-cells as evidenced by IFN-γ ELISPOT (Fig 4). Weak and transient antibody responses were detected (data not shown). No specific T-cells were detected in mucosal biopsies (data not shown)

After SIVmac251 rectal challenge:

Immune response:

T-cell responses increased significantly earlier (1 & 2 weeks pc) in blood and at higher levels in both vaccinated groups when compared to controls (Fig.5). The highest responses were detected in the group vaccinated ID+EP. T-cell responses also increased in rectal biopsies (Figure not shown).

Viremia:

AUC (days 0-70) of plasma viral load was significantly reduced ($p=0.0093$) only in the ID+EP group (Fig.5 & 6).

Conclusion

1. Auxo-GTU[®]-MultiHIV/SIV DNA induced strong and long lasting T-cell responses in macaques.
2. Electroporation associated to ID enhances vaccine immunogenicity.
3. Significant control of uncloned pathogenic SIVmac251 was observed after a single rectal challenge with a high dose of virus.

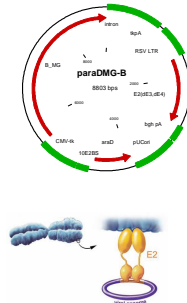


Fig.1: Auxo-GTU[®]-MultiHIVB & Auxo-GTU[®]-MultiSIV DNA vaccines. Adult cynomolgus macaques have been injected at weeks 0, 4 and 12 with 1 mg of the vaccine either by ID or by ID+EP route

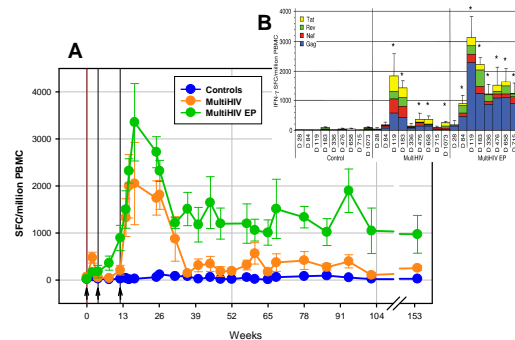


Fig.2: T-cell responses (IFN-γ ELISPOT) in animals vaccinated with Auxo-GTU[®]-MultiHIVB by ID route with or without EP. 4 animals in each group have been vaccinated at weeks 0, 4 and 12 with 1 mg of the DNA vaccine. Fresh isolated PBMC have been stimulated for 18h with pools of 15 mer peptides (overlapping of 11 AA). A) cumulative response to Gag, Rev, Tat and Nef. B) response to individual antigens. *Martinson et al, Hum Gene Ther, 2009*

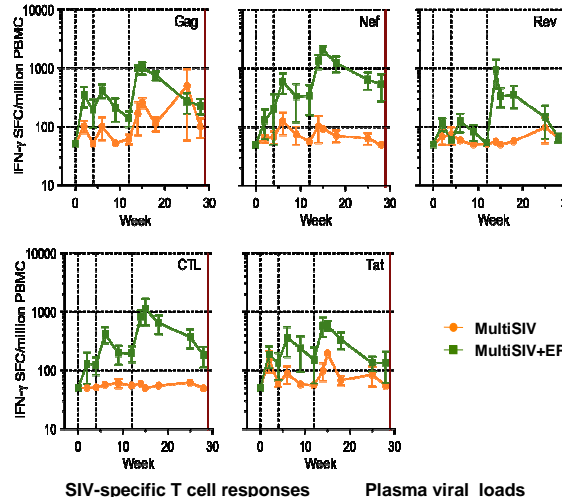


Fig.3: Production of P24 HIV Gag as visualized with anti-Gag-FITC MoAb in skin biopsies 24h after ID injection (±EP) of macaques with Auxo-GTU[®]-MultiHIVB. Antigen presenting cells have been stained with Alexa700 anti-HLADR antibody.

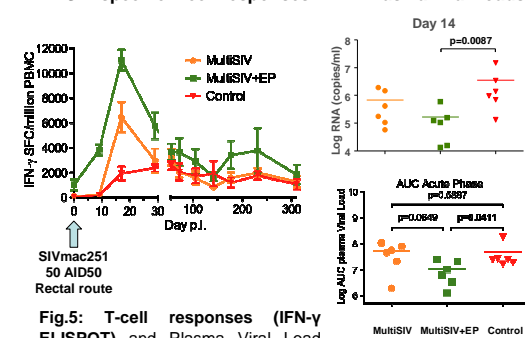


Fig.4: T-cell responses (IFN-γ ELISPOT) in animals vaccinated with Auxo-GTU[®]-MultiSIV by ID route with or without EP. 6-8 animals in each group have been vaccinated at weeks 0, 4 and 12 with 1 mg of the DNA vaccine. Fresh isolated PBMC have been stimulated for 18h with pools of 15 mer peptides (overlapping of 11 AA). A) cumulative response to Gag, Rev, Tat and Nef. B) response to individual antigens.

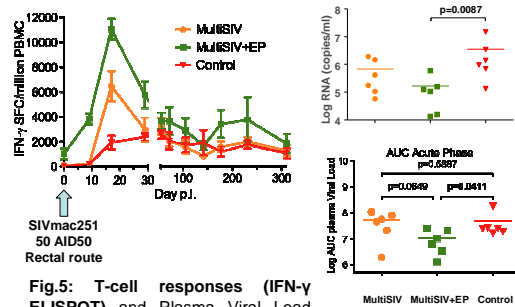


Fig.5: T-cell responses (IFN-γ ELISPOT) and Plasma Viral Load (gag RT-PCR) in macaques challenged at week 29 with SIVmac251

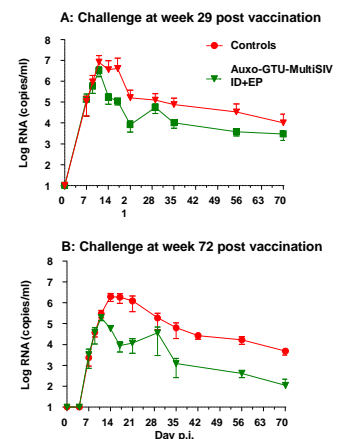


Fig.6: Plasma Viral Load (gag RT-PCR) in macaques challenged at week 29 and 72 with SIVmac251